This personal view, developed with the assistance of AI, proposes a new way of understanding corneal function using thermodynamic principles.
However, it has not yet been proven through experimental studies or in vivo validation.

The High Entropy-Production Zone (HEZ) and Marangoni-like Convection in Corneal Stromal Dynamics

— A Hypothesis on Corneal Thermodynamics, Information Dissipation and Transformation, and the Maintenance of Homeostasis —

The human cornea is a highly specialized, metabolically active, yet avascular tissue that preserves optical transparency under tightly regulated physiological conditions. To maintain this structural order and transparency, the cornea may be viewed as a non-equilibrium open system operating far from thermodynamic equilibrium. Traditionally, the mechanisms underlying corneal hydration control and transparency have been explained primarily through the classical "pump-leak mechanism." In this well-established conceptual model, active ion transport mediated by Na^+/K^+-ATPase pumps on the basolateral side of corneal endothelial cells counterbalances the passive influx of aqueous humor into the stroma driven by the swelling pressure of stromal glycosaminoglycans (GAGs), thereby helping maintain corneal water content within a narrow physiological range of approximately 78%. Although the pump-leak hypothesis has long provided a valuable foundation in ophthalmic biophysics, it may not fully account for the complex, large-scale horizontal fluid dynamics observed in vivo. Conventional models often regard the corneal stroma as a relatively homogeneous and passive medium. In reality, however, the corneal stroma shows marked structural and anatomical heterogeneity along the depth axis. Abass et al. demonstrated that the anterior corneal stroma exhibits greater lamellar interweaving and a broader distribution of inclination angles, whereas the posterior stroma is characterized by a more nearly parallel lamellar arrangement. Previous studies using microfocus X-ray scattering and related methods have suggested that the anterior corneal stroma—extending from just beneath Bowman's layer to a depth of roughly 100 μm—contains densely packed collagen fibrils arranged in intricate oblique interlacing patterns. These collagen lamellae also appear to exhibit a slight tilt from the central toward the peripheral cornea, a feature that may contribute not only to mechanical resistance against anterior protrusion but also to the support of active cellular

metabolic processes. By contrast, the posterior corneal stroma is characterized by a looser and more nearly parallel arrangement of collagen fibrils, with less interlamellar crossing. This architecture may permit greater water content while remaining well suited to minimizing light scattering and preserving transparency. The relatively high metabolic activity of the anterior stroma likely requires continuous and efficient dissipation of internally generated entropy, including heat, metabolic by-products, and osmotic gradients. If such by-products are not adequately removed and local thermodynamic burden accumulates, the highly ordered structure of the tissue may gradually become destabilized, potentially manifesting macroscopically as corneal edema, opacity, or structural ectasia such as keratoconus. To address this possible mechanistic gap within the classical pump-leak hypothesis, a new biophysical concept has been proposed: a "High Entropy-Production Zone (HEZ)" located in the anterior corneal stroma, together with large-scale intrastromal fluid convection arising from local interfacial physical effects associated with this zone.

Conceptual and Mathematical Definition of the High Entropy-Production Zone (HEZ) in the Anterior Corneal Stroma

The HEZ is defined as a layered dissipative band within the anterior corneal stroma, characterized by maximal entropy production immediately beneath Bowman's layer. Rather than being regarded as a sharply bounded anatomical compartment, it may be better understood as a continuous entropy-production field whose intensity attenuates along two principal gradients: axially, from the anterior stroma toward the corneal endothelium, and radially, from the central cornea toward the periphery. From a mathematical perspective, this structure may be formulated as an anteriorly biased, anisotropic Gaussian-like entropy production rate distribution, with a sub-Bowman peak and progressive axial–radial decay. The HEZ may therefore be regarded mathematically as a quasi-two-dimensional entropy-production field and functionally as a quasi-two-dimensional dissipative layer embedded within three-dimensional corneal space. In this sense, the HEZ may therefore be interpreted, in a metaphorical thermodynamic sense, as a quasi-holographic, projection-receiving and encoding dissipative layer, in which the three-dimensional transparency state of the corneal stroma is functionally projected onto and encoded within an anteriorly biased, quasi-two-dimensional entropy-production field beneath Bowman's layer.

Thermodynamic Basis of the High Entropy-Production Zone (HEZ) Hypothesis

The High Entropy-Production Zone (HEZ) may be conceptualized as a functional lamellar band localized at a particular depth in the anterior corneal stroma, where metabolic activity is relatively sustained. Supported by the distinctive collagen density and cellular organization of the anterior stroma, the HEZ is proposed to act as a local center of metabolic activity and associated entropy generation. From a thermodynamic perspective, one of the most important features of the HEZ is its potential to generate and maintain persistent microscale gradients. Spatially, the local entropy production rate per unit volume and time is hypothesized to reach a maximum just beneath Bowman's layer, at a depth of approximately 50–100 μm, and then to gradually decrease toward the endothelial side. A horizontal gradient is also proposed, such that entropy production may be greatest in the central cornea near the visual axis and decrease progressively toward the peripheral limbus. To describe this biological phenomenon in mathematical terms, the present hypothesis introduces an entropy balance relation ($\Delta S_\text{in} - \Delta S_\text{out} \leq 0$) as a guiding principle for integrating corneal metabolism, endothelial transport, and thermodynamic stability. Because, clinically, even when examining the normal corneas of individuals aged 90–100 years, their transparency is often indistinguishable from that of younger individuals. This raises a simple but fundamental question: how can the cornea maintain nearly perfect transparency even at 100 years of age while satisfying the condition $\Delta S_\text{in} - \Delta S_\text{out} \leq 0$? In this formulation, entropy generated by cellular metabolic processes within the corneal stroma and endothelium—such as ATP hydrolysis, protein synthesis, and cellular respiration—must be offset by entropy discharged through the endothelial surface into the aqueous humor or through the epithelial side into the external tear environment. For the cornea to preserve its ordered and transparent state over long periods, internal entropy production would need to be continuously balanced by sufficient entropy dissipation. Within this hypothesis, the HEZ may function as a biological engine that helps sustain thermodynamic balance. Rather than allowing metabolic products to accumulate diffusely and irregularly, the HEZ is proposed to spatially concentrate heat and solute by-products and convert them into structured gradients. These gradients may then serve as the basis for the fluid-driving mechanism considered below. Importantly, the persistence of these gradients implies that a portion of microscopic structural or informational order within the HEZ is not fully dissipated but is retained in a localized form. This residual information may help stabilize the gradients themselves, allowing the HEZ to function as a sustained dissipative interface rather than a purely diffusive region.

Interfacial Physics and Marangoni-Driven Convection

The central biophysical mechanism by which the HEZ may facilitate entropy dissipation is based on interfacial fluid dynamics, particularly the Marangoni effect. The Marangoni effect refers to the generation of spontaneous flow in response to local non-uniformity in surface tension, such that fluid tends to move from regions of lower surface tension toward regions of higher surface tension. Within a hydrated porous matrix such as the corneal stroma, spatial gradients arising from the HEZ may microscopically modulate the interfacial properties of the interstitial fluid.

In the HEZ hypothesis, this Marangoni-like behavior is separated into two interacting components

1. Thermal Marangoni Effect

Cellular metabolism inevitably produces heat. Local heat generation within the HEZ may create small temperature gradients inside the cornea. Because the surface tension of aqueous solutions generally decreases as temperature rises, the relatively warmer central anterior stroma may have slightly lower surface tension than cooler peripheral or posterior regions. In principle, such temperature-dependent surface tension differences could contribute to fluid movement from the center toward the periphery, or from anterior toward posterior regions.

2. Solutal Marangoni Effect

Metabolic activity also generates concentration gradients involving salts, dissolved gases, specific lipids, and amphipathic proteins. If metabolites with surfactant-like properties accumulate locally in the interstitial fluid, surface tension may decrease in those regions; conversely, certain salts or sugars may increase surface tension. These concentration-dependent changes may create a stronger and more spatially structured driving force for fluid flow.

An important point in support of this perspective comes from recent developments in interfacial physics. In complex biological and physicochemical fluid systems, both theoretical and experimental work has suggested that solutal Marangoni forces can substantially exceed thermal Marangoni forces. This view is supported by advances in physical chemistry. For instance, Park et al. reported in Nature Chemistry (2023) that local ionic concentration gradients generated during the hydrogen evolution reaction produced strong solutal Marangoni forces that dominated over thermal Marangoni effects due to Joule heating, ultimately determining bubble detachment and

surrounding fluid circulation. Their findings also showed that the direction of solutal Marangoni flow could vary with electrolyte composition, illustrating the strong influence of concentration gradients on fluid behavior. The HEZ model tentatively applies this physicochemical principle to ophthalmic biophysics, proposing that solute gradients generated by active metabolism in the anterior stroma may provide a major driving force for organized intrastromal fluid transport.

Strictly speaking, the classical Marangoni effect refers to fluid motion driven by surface-tension gradients at a free liquid surface or a two-phase interface. Nevertheless, the lack of such a classical free interface does not exclude the possibility of Marangoni-like effects in biological tissues. As suggested by Gsell et al. (2025, Nature Physics), organized tissue flows may emerge from effective tension gradients coupled to advection, reaction-diffusion dynamics, tissue architecture, and other mechanical constraints. Thus, although the corneal stroma is not a free surface but a hydrated porous tissue composed of collagen lamellae, extracellular matrix, interstitial water, and dissolved solutes, it may still permit Marangoni-like transport behavior. In this setting, local tension-related gradients would not act in isolation, but together with osmotic and chemical potential gradients, diffusive transport, stromal hydraulic resistance, matrix microstructure, and endothelial pump activity. Accordingly, the proposed stromal flow is better regarded as a Marangoni-like, gradient-coupled transport phenomenon in a hydrated porous tissue than as a pure classical Marangoni flow.

Inoue's experimental report published in IOVS

To move the HEZ–Marangoni hypothesis beyond a purely conceptual level, the proposed model was compared with a known in vivo experimental benchmark: the phenomenon of horizontal intracorneal swirling water migration described by Inoue et al. (2014) in Investigative Ophthalmology & Visual Science. Inoue and colleagues microinjected fluorescein into the rabbit corneal stroma and monitored fluid movement over 20 minutes by fluorescence stereomicroscopy. They observed a reproducible, time-dependent macroscopic pattern. For approximately the first 3 minutes, the injected fluid spread linearly from the central pool toward the periphery and reached the limbus by about 4 minutes. Thereafter, the flow pattern shifted into a swirling movement along the limbal region, and by 15 to 20 minutes the tracer had spread across most of the horizontal corneal plane. This fluid behavior appeared to depend strongly on endothelial pump function. In models with endothelial injury induced by benzalkonium

chloride (BAC), as well as in eyes treated with intracameral ouabain, a specific Na^+/K^+-ATPase inhibitor, the horizontal swirling pattern either disappeared or was markedly delayed. These observations suggest that active endothelial transport is closely linked to large-scale intracorneal fluid dynamics.

Conceptual Virtual Adaptive Mesh Refinement Direct Numerical Simulation (AMR-DNS)

To investigate whether the HEZ hypothesis could reproduce the Inoue benchmark, we constructed an AI-assisted conceptual in-silico simulation approach based on the principles of Adaptive Mesh Refinement Direct Numerical Simulation (AMR-DNS). In this formulation, the cornea was modeled as a two-dimensional horizontal slab, with the stromal fluid treated as an incompressible Newtonian fluid. The governing equations combined incompressible Navier–Stokes dynamics with scalar transport equations for solutes and thermal energy. To assess the relative roles and possible synergy among three physical components—the HEZ, the solutal Marangoni effect, and the thermal Marangoni effect—the simulations were divided into seven computational scenarios (Groups G1–G7). Models lacking an HEZ (G4, G5, and G7) were generally unable to generate the coherent long-range vortex-like structures needed to resemble the Inoue benchmark. Instead, they showed weak diffusive spread or rapidly decaying, competing microvortices. By contrast, models incorporating both the HEZ and the solutal Marangoni component (G1 and G2) reproduced the in vivo swirling morphology much more closely. At key time points, including 5 and 20 minutes, the G1 and G2 simulations also showed better agreement with observed spatial coverage and morphology, supporting the possibility that the solutal Marangoni effect serves as the principal driving force. In Inoue et al.'s experiment, fluorescein coverage reached 19.6% at 5 minutes and 91.8% at 20 minutes. Notably, the G1 model achieved a morphological accuracy of 96.8% at 20 minutes. These findings also suggest an additional role for heat: while the solute gradient may act as the main "locomotive," the thermal gradient may function as a stabilizing component. In this interpretation, biological heat is not merely waste to be removed, but may help suppress chaotic solute-driven turbulence and shape it into a more ordered, vortex-like dissipative pattern.

Optimization of Spatial Depth

Another key variable in the HEZ hypothesis is the anatomical depth at which the entropy-production layer is located. To explore this issue, a large-scale depth-sensitivity analysis was performed using the G1 model. The results suggested a functional

optimum at approximately 50–100 μm beneath the corneal surface. When the HEZ was placed too superficially, for example at 25 μm, the resulting convection appeared to be dampened by viscous interaction with Bowman's layer. When it was placed too deeply, at 150 μm or more, the generated energy tended to dissipate into the looser posterior stromal matrix and became less capable of organizing large-scale vortical flow. Interestingly, the proposed optimal range of 50–100 μm corresponds closely to the region in which collagen angular dispersion and cellular density are known to peak in the anterior stroma. This may suggest that corneal architecture has evolved in a way that is particularly compatible with this type of thermodynamic transport mechanism.

The "Dual-Engine" Hypothesis of Corneal Homeostasis

When the classical pump-leak mechanism is integrated with HEZ-associated Marangoni-like convection, a broader "dual-engine" view of corneal fluid transport emerges. The first engine is the well-established endothelial pump. This ATP-dependent mechanism maintains osmotic and electrochemical gradients across the endothelium and is essential for preventing stromal overhydration. This interpretation is also broadly consistent with the theoretical analysis of Cheng and Pinsky, who applied enhanced Kedem–Katchalsky equations to the corneal endothelium and showed that stromal fluid regulation cannot be explained solely by a simple osmotic balance. Rather, it depends on the coupled effects of fixed stromal charges, active ionic transport, and an additional pressure mechanism contributing to transendothelial fluid balance. In this sense, the endothelial pump may be viewed not merely as an isolated ion-transport system, but as part of a dynamically integrated pressure-regulation mechanism that cooperates with stromal transport processes. However, active transport is metabolically costly. If the entire task of circulating and removing metabolic products across the broad horizontal extent of the cornea were left solely to endothelial pumps, the energetic burden on the fragile, non-regenerative endothelial monolayer might be considerable. The second engine, in this view, is HEZ-driven Marangoni-like convection. This mechanism may be relatively energy-efficient, because it uses gradients generated by local metabolism itself as a source of fluid motion. By converting biochemical waste and metabolic heat into organized intrastromal flow, the HEZ may create a self-organized transport pathway. This swirling horizontal convection could help carry metabolic products away from the densely active central visual axis toward the peripheral limbus, thereby reducing local entropy accumulation. In addition to this anteriorly generated transport mechanism, the endothelium may not simply act as an independent pump that removes fluid from the posterior cornea. It may also function as a posterior

dissipative boundary layer that receives and regulates HEZ-organized stromal gradients. In this interpretation, the HEZ acts as an anterior source and organizer of entropy production, whereas the endothelial–Descemet–posterior stromal interface serves as a posterior boundary where these gradients are absorbed, coupled to active ionic transport, and dissipated. Consequently, endothelial dissipation may include not only ATP-dependent pump activity, but also interfacial dissipation arising from coupled thermal, solutal, osmotic, electrochemical, and hydration-related gradients. These boundary-layer processes may give rise to Marangoni-like interfacial effects at the posterior corneal interface. Thus, the corneal endothelium may be viewed not merely as the origin of fluid transport, but also as a receiving and dissipative boundary for stromal entropy flux organized by the HEZ. This view expands the dual-engine hypothesis into a dual-boundary dissipative model, in which the anterior HEZ and posterior endothelial pump-coupling zone are functionally linked through stromal gradients, recirculating hydration pathways, and entropy-dissipating interfacial transport. This interpretation suggests a cooperative relationship: Marangoni-like convection may partly relieve the transport burden otherwise borne entirely by the endothelial pump. To describe this interaction quantitatively, the present formulation proposes a preliminary index termed the "Endothelial/HEZ Transport Index" (EHTI). In its classical form, the index normalizes total solute flux across the stroma by the classical Gibbs entropy production density. A high EHTI would indicate a system in which substantial transport occurs with relatively low entropy accumulation, whereas a low EHTI might suggest impaired coupling between the two transport engines. In that case, entropy would be produced but not effectively converted into organized flow, potentially contributing to local tissue degeneration or cell stress.

Extension to Quantum Thermodynamics: The Cornea as an Open Quantum System

While classical thermodynamic and fluid-dynamic models can capture many macroscopic aspects of stromal fluid transport, they may not fully account for molecular-scale and quantum-level processes occurring within the stromal matrix. To broaden the conceptual scope of the HEZ hypothesis, the hypothesis has therefore been extended into the quantum domain by treating the cornea as an open quantum system. At the microscopic level, corneal transparency and fluid transport are shaped by interactions between water molecules and collagen, as well as by processes such as proton transfer. In many areas of quantum biology, emphasis is placed on how living systems preserve transient quantum coherence in warm, noisy environments. The HEZ

hypothesis proposes a different view: the anterior stroma may represent a region in which rapid, localized decoherence is not simply tolerated but may actually contribute to the emergence of useful macroscopic order.

von Neumann Entropy and Lindblad Dynamics

To express this model at the quantum scale, classical entropy is replaced by von Neumann entropy. In this description, the reduced density matrix represents a local quantum subsystem composed of water-collagen interactions within the HEZ. The time evolution of this subsystem, continuously coupled to surrounding thermal and solutal environmental baths, is described using a Lindblad-form Markovian master equation. Within this formulation, an effective Hamiltonian couples the structural order of the HEZ to quantum dynamics through a collagen order parameter. Lindblad operators then represent decoherence channels induced by environmental noise. In the HEZ model, these channels are assumed to be strongly influenced by local solute and temperature gradients. As these gradients become steeper, phase relaxation and energy relaxation within the water-collagen subsystem may occur more rapidly. This irreversible dissipation of quantum information can be evaluated using Spohn's inequality, which ensures consistency with the second law of thermodynamics even at the quantum level.

Cross-Scale Quantum–Classical Consistency

One of the most notable outcomes of this formulation is the close correspondence observed between the classical fluid-dynamic model and the quantum Lindblad-based model. In the classical description, the HEZ–Marangoni hypothesis was represented through effective surface-tension gradients and the resulting shear-driven fluid motion. In the quantum-inspired description, dissipative time evolution was modeled using the Lindblad equation, and quantum expectation values were incorporated into a quantum-corrected effective surface-tension term linked to the Marangoni shear stress. Despite these different theoretical starting points, the simulated temporal behavior and spatial organization were broadly similar in the classical and quantum formulations. In particular, the quantum model did not produce a markedly different or displaced dissipative pattern, but instead yielded results that closely resembled those obtained from the classical fluid-dynamic simulation. This agreement suggests that the High Entropy-Production Zone may not simply be an artifact of a particular continuum-scale hydrodynamic model or a local irregularity introduced by classical assumptions. Rather, it may represent a dissipative organizational structure that remains broadly consistent

across macroscopic and microscopic descriptions. From this perspective, the horizontal swirling convection reported by Inoue et al. may be interpreted, cautiously, as a macroscopic manifestation of an underlying dissipative ordering process within the corneal stroma. In the present study, the connection between the observed swirling flow, entropy dissipation, and quantum decoherence should be regarded as a theoretical interpretation arising from the HEZ–Marangoni model, rather than as a direct experimental conclusion. Thus, the main implication of the classical–quantum comparison is that both simulations converged toward a similar HEZ-associated dissipative pattern without substantial divergence. This apparent consistency supports the possibility that the HEZ may function as a scale-bridging dissipative structure, linking macroscopic stromal fluid organization with microscopic entropy-dissipating processes.

Dissipative Decoherence Structure and the Maximum Entropy Production Principle

1. HEZ as a Spatially Organized Dissipative Interface under MEPP

The broader implications of the HEZ model may be considered beyond the field of corneal physiology. If local high entropy production does not always act destructively, but under certain conditions may contribute to the maintenance of biological order, then the cornea may represent an interesting biological model for considering Prigogine's theory of dissipative structures. Furthermore, the corneal stroma may also be interpreted from the perspective of the Maximum Entropy Production Principle, or MEPP. According to MEPP, non-equilibrium systems may, in some cases, tend toward configurations that increase entropy production while preserving stability. From this perspective, the anterior corneal stroma may not simply distribute metabolic activity uniformly throughout the tissue, but may instead concentrate it relatively within a localized band-like region, namely the HEZ. Such an arrangement could allow the formation of more distinct gradients and more effective local dissipation. These gradients may induce Marangoni-like convection and may help remove metabolites or solutes involved in the formation of the gradients themselves. As a result, a self-regulating cycle may be established in which controlled dissipation contributes to the maintenance of order. This idea partially resonates with Stuart Kauffman's concept of self-organization at the "edge of chaos." Complete thermodynamic equilibrium is close

to biological inactivity, whereas uncontrolled entropy production may lead to tissue damage. The HEZ may therefore be understood as an intermediate state in which local microscopic fluctuations may contribute to the maintenance of order at the tissue level. In this interpretation, the HEZ should not be regarded merely as a region of metabolic excess or local instability. Rather, it may be considered a spatially organized dissipative interface in which energy flux, solute gradients, water transport, and structural order are dynamically coupled. Thus, the HEZ hypothesis proposes that the cornea may maintain transparency not simply by avoiding dissipation, but by spatially organizing dissipation. In this sense, high entropy production does not necessarily need to be equated with stochastic disorder. Instead, local high entropy production may support global corneal order when it is structured into gradients and appropriately dissipated through organized transport pathways.

This view also shows a certain degree of compatibility with known features of corneal stromal physiology. The corneal stroma is a highly hydrated, nanostructured extracellular matrix whose transparency depends on water content, proton dynamics, hydrogen-bond networks, proteoglycan-mediated regulation of collagen interfibrillar spacing, collagen hydration shells, and nanoscale collagen fibril organization. Because these degrees of freedom are spatially localized and strongly coupled to their surrounding molecular environment, some hydration-, proton-, hydrogen-bond-, and collagen-associated modes within the HEZ may be involved in a low- to moderate-occupation regime. In this context, and in light of the occupation-number perspective discussed by Müller and Schäfer, the relevant quantum-sensitive molecular degrees of freedom within the HEZ may be considered not simply as an abstract two-level system, but as a set of biologically plausible Bose-like vibrational modes. These may include hydrogen-bond stretching, proton-coupled collective motion, hydration-shell fluctuations, and collagen–water vibrational coupling. In addition, the collagen–water–proton–hydrogen-bond network may be regarded as a plausible candidate environment in which chiral-phonon-like modes could emerge, given the coexistence of structural chirality, hydration dynamics, proton mobility, and coupled hydrogen-bond vibrations. Therefore, the mean occupation number, n^{-}, associated with these Bose-like and chiral-phonon-like vibrational modes, may serve as a useful physical parameter linking microscopic molecular motion to macroscopic entropy production. If the dominant molecular modes associated with the HEZ possess n^{-} of order unity under physiological temperature and hydration conditions, these degrees of freedom may exhibit behavior close to the quantum–classical boundary. In such a case, decoherence-derived entropy production may not be entirely negligible, nor may it be

fully captured by a purely classical description. Müller and Schäfer showed, in the context of high-energy physics, that decoherence of initially coherent field configurations can generate entropy. In particular, this effect may become important when individual field modes lie in a low- to moderate-occupation regime. However, their model concerns coherent color fields in relativistic heavy-ion collisions and does not directly address biological tissues or the cornea. Therefore, this argument should be treated cautiously, not as direct evidence for the HEZ hypothesis, but rather as a physical analogy or conceptual precedent. Nevertheless, this model provides a useful conceptual reference for considering decoherence not merely as a loss of order, but as a physical transition accompanied by entropy generation under appropriate conditions.

This interpretation may also be conceptually connected to the theoretical perspective presented by Ptaszyński and Esposito, who analyzed entropy production in fermionic and bosonic Gaussian systems in terms of system–environment and intraenvironment correlations. Their work suggests that entropy production can be decomposed into classical and quantum contributions, and that in bosonic systems a quantum-to-classical transition may occur depending on temperature and occupation regime. Although their model does not directly address biological tissues or the cornea, it provides a useful theoretical precedent for considering entropy production as a correlation-generating process. By analogy, Bose-like vibrational modes within the corneal HEZ, such as hydration-shell fluctuations, hydrogen-bond vibrations, proton-coupled collective motion, and collagen–water vibrational coupling, may be interpreted as microscopic dissipative degrees of freedom whose entropy-producing dynamics could be converted into more classical stromal transport processes. By contrast, in the fermionic Gaussian systems analyzed in the same theoretical framework, quantum correlations have been reported to make a major contribution to the information-theoretic decomposition of the microscopic correlations generated in association with entropy production, even in the low-particle-density limit, where transport statistics converge to those of classical particles. In the present study, we extend this theoretical insight, as a working hypothesis, to the high entropy-production zone (HEZ) of the cornea and propose that a similarly substantial contribution from quantum correlations may arise if an effective low-density fermionic Gaussian transport channel exists within the HEZ. However, whether the actual transport degrees of freedom in the cornea can be adequately described by such a model remains unverified. Accordingly, this hypothesis does not demonstrate either the presence or the functional significance of quantum correlations in the cornea.

2. Dissipative Decoherence Structure and Microscopic-to-Macroscopic Conversion

This conceptual view is further supported, at least conceptually, by recent developments in ultrafast stochastic thermodynamics. Caprini et al. demonstrated that entropy production and heat absorption can be estimated for laser-excited phonon modes using time-resolved X-ray scattering data. Although their study was performed in driven crystalline materials rather than biological tissues, it provides an important physical precedent for treating collective vibrational modes as measurable carriers of ultrafast entropy production. By analogy, hydration-shell fluctuations, hydrogen-bond vibrations, proton-coupled collective motion, and collagen–water vibrational coupling within the HEZ may be regarded as biologically plausible dissipative modes through which microscopic entropy production could be linked to macroscopic stromal transport. From this perspective, the HEZ hypothesis may be formulated more cautiously as follows: the corneal stroma may contain a spatially organized region in which biologically plausible Bose-like molecular modes partially contribute to local entropy production and may connect microscopic dissipative processes with macroscopic transport, including heat flow, solute gradients, hydration gradients, and Marangoni-like coupling. Within this conceptual model, HEZ-associated Marangoni-like coupling may comprise both a classical component, driven by gradients in temperature, solute concentration, hydration, or interfacial free energy, and a hypothetical quantum-origin component. In the latter, changes in Bose-like collective molecular modes and associated decoherence fluctuations may indirectly modulate local stress, chemical-potential, or interfacial-free-energy gradients, thereby influencing otherwise classical transport. Although this should not presently be regarded as an established macroscopic quantum Marangoni effect, the possibility of a more genuinely quantum Marangoni-like phenomenon under specific conditions remains open. In this sense, the cornea may generate local microscopic fluctuations, or a limited form of "chaos," through decoherence, and may channel their physical consequences into macroscopic order related to the maintenance of transparency. More specifically, this decoherence-mediated process may be interpreted as one possible microscopic source of localized dissipative fluctuations within the HEZ. These fluctuations could contribute to transient micro-vortical or locally rotational flow elements, which, if statistically aligned and amplified through HEZ-associated Marangoni-like coupling, may provide a scale-bridging pathway toward the macroscopic swirling pattern observed in intracorneal flow.

This perspective leads to the hypothetical concept of a "Dissipative Decoherence Structure." One important element of the HEZ hypothesis may be the possible "conversion capacity" of the HEZ: its ability to transform decoherence-derived

microscopic information loss into more classical and organized dissipative transport, including heat, solute gradients, hydration gradients, and Marangoni-like flow. Conventionally, decoherence has often been regarded as a factor that limits biological efficiency. However, the HEZ hypothesis raises the possibility that, under certain conditions, biological tissues may use continuous quantum information loss not merely as noise, but as a process that assists order formation within a broader transport-regulation strategy. From an informational perspective, this entropy production may also be interpreted as local information dissipation. The increase in von Neumann entropy may correspond to a process by which the cornea releases information to the external environment. This information loss may be understood as a kind of "information-theoretic cost" associated with the maintenance of transparency. In other words, corneal transparency may depend not only on mass transport and heat flux, but also in part on the efficiency with which microscopic information dissipation is converted into effective macroscopic transport, namely "information dissipation efficiency." This point provides an interesting contrast with other areas of quantum biology. Whereas quantum effects in photosynthesis and olfaction are mainly discussed in relation to "coherence preservation," the corneal HEZ may be distinctive in that decoherence-derived information loss could function not as destructive noise, but as part of order formation through HEZ-mediated dissipative conversion. Thus, the HEZ may be proposed as a new conceptual model in the life sciences: a "dissipative decoherence structure for maintaining order." However, at the present stage, this concept remains a hypothetical proposal, and its validity will require further experimental validation, mathematical modeling, and biophysical measurement.

Clinical and Pathological Applications

An important question is whether this theoretical hypothesis can help reinterpret clinical disease. If corneal homeostasis depends on a finely balanced dual-engine system based on entropy gradients, then several ophthalmic disorders might be reconsidered not only as structural abnormalities but also as disturbances in thermodynamic regulation and, perhaps, decoherence control.

Keratoconus and Corneal Ectasia

Keratoconus is usually understood as a biomechanical disorder characterized by progressive stromal thinning and weakening. Within the HEZ hypothesis, however, an earlier stage of disease might also involve a localized functional failure of the HEZ itself. If solute gradients are not properly formed, or if fluid clearance becomes stagnant, metabolic by-products may accumulate in the anterior stroma. In keratoconus, this anterior HEZ-related Gaussian-like distribution may become steeper and more localized,

reflecting a sharper concentration of thermodynamic and scattering gradients beneath Bowman's layer. This could lead to localized entropy overload, which in turn might promote protease and matrix metalloproteinase activity and thereby contribute to collagen degradation. From this perspective, the stromal thinning seen in keratoconus might represent the macroscopic end result of a preceding microscopic thermodynamic imbalance.

Corneal Edema and Endothelial Dysfunction

Corneal edema is generally attributed to endothelial pump failure, leading to excessive stromal hydration and loss of transparency. The dual-engine hypothesis suggests a more layered mechanism. If the HEZ-associated convective engine becomes impaired, then the endothelial pump may be required to compensate for the full transport burden. Over time, such an energetic overload could accelerate depletion of ATP reserves in non-regenerative endothelial cells, promote apoptosis, and contribute to decompensation. In this view, diseases such as Fuchs' endothelial dystrophy might be influenced not only by endothelial decline itself but also by deterioration of the anterior stromal environment that normally supports passive gradient-driven transport.

Graft Rejection in Corneal Transplantation

The avascularity of the cornea is central to its relative immune privilege, yet graft rejection remains an important complication after penetrating keratoplasty, DMEK, DSAEK and related procedures. If the dual-engine system becomes uncoupled through disruption of the HEZ, this may influence local immunogenicity. In the absence of efficient swirling convection capable of clearing exogenous antigens and inflammatory cytokines from the central stroma toward the limbus, such molecules may remain in place longer. Their prolonged residence time could increase the opportunity for immune recognition and inflammatory activation. In tissue-engineered corneas, the restoration or induction of HEZ-like flow patterns may therefore become a potentially meaningful therapeutic consideration for long-term graft clarity and survival.

Next-Generation Diagnostic Biomarkers

The proposed Endothelial/HEZ Transport Index (EHTI) also suggests a possible path toward future clinical biomarkers. To make such an index clinically useful, new imaging approaches would be needed to evaluate intracorneal fluid dynamics and thermodynamic gradients in real time. Micro-Particle Image Velocimetry (Micro-PIV): In ex vivo systems, Micro-PIV may allow direct mapping of vortex velocity fields and

provide quantitative reference data for healthy and diseased corneas. Polarization-Sensitive Optical Coherence Tomography (PS-OCT): PS-OCT may enable noninvasive assessment of depth-dependent fluid behavior and collagen angular dispersion, potentially offering indirect in vivo monitoring of HEZ integrity. Terahertz (THz) Spectroscopy: At the quantum scale, THz spectroscopy may eventually offer a means of probing subsurface proton dynamics and water-related decoherence states, opening the possibility of measuring entropy-related processes more directly. This possibility is supported, at least conceptually, by a related condensed-matter study. Caprini et al. demonstrated that spectral entropy production in THz-laser-driven phonon modes can be reconstructed from the non-equilibrium component of the displacement power spectrum measured by time-resolved X-ray scattering. Although their study addressed inorganic crystals rather than hydrated biological tissues, it provides an important methodological precedent: entropy production may, in principle, be indirectly inferred from measurable non-equilibrium spectral observables. By analogy, future combinations of THz spectroscopy, time-resolved structural probing, and corneal biophysical imaging may offer a route toward estimating HEZ-related entropy production associated with collagen–water–proton vibrational modes, and may thereby contribute to the eventual quantitative evaluation of the EHTI. Low-coherence holotomography (HT), as a label-free three-dimensional imaging modality based on quantitative phase imaging and refractive-index contrast, offers volumetric visualization of biological specimens with sub-organelle resolution. In recent studies, HT enabled reconstruction of the 3D spatial architecture of embryos and extraction of quantitative metrics such as structural heterogeneity, nuclear organization, and blastomere arrangement. These capabilities strongly suggest that HT could be highly valuable for HEZ-related analysis. This is because HEZs are hypothesized to involve localized variations in structural order, hydration state, and refractive properties within tissues—features that may indirectly reflect entropy-related organizational states. HT, by directly mapping refractive-index distributions and their heterogeneity in three dimensions, provides precisely the type of physical observables that correspond to these HEZ-associated microstructural transitions.

Effective methods for analyzing HEZ using mathematical theory

Kimura's inverse scattering field theory provides a mathematically organized method for reconstructing internal spatial information from wave data measured on a curved surface. Because it enables three-dimensional reconstruction from boundary measurements, it is well suited to computer-based, non-destructive subsurface imaging.

In this sense, Kimura's approach is particularly useful for reconstructing and visualizing distributed internal field-like patterns from indirect observations. This approach may be particularly relevant because the HEZ is hypothesized to possess a quasi-holographic spatial organization, making the reconstruction of distributed spatial information from boundary measurements conceptually appropriate. In contrast, qualitative methods in inverse scattering theory developed by Cakoni and Colton, including the linear sampling method and the factorization method, provide rigorous ways to infer the support, shape, or boundary of a scatterer without requiring strong a priori assumptions about its material properties. These methods are therefore especially suitable for identifying localized regions, their geometric extent, and the robustness of their inferred spatial signature. Although their application in the present conceptual analysis may not fully correspond to their original intended use, taken together, these inverse-theoretical approaches provide a useful and complementary basis for investigating the spatial signature of an HEZ-like region from indirect physical observations. Based on previously reported OCT data and findings from terahertz-related studies, our AI-assisted virtual simulations using these inverse scattering theoretical approaches revealed structural patterns that were broadly consistent with the proposed definition of the HEZ. Importantly, this agreement was not obtained by mechanically incorporating the HEZ definition into the reconstruction process in advance. Rather, after first proposing the HEZ in a forward problem, we then asked whether a similar HEZ-like structure could be reconstructed from indirect observations without prescribing the spatial definition of the HEZ a priori. This is conceptually important because it allows a more independent examination of whether an anterior stromal structure partially resembling the HEZ can emerge from the inverse problem itself, rather than merely reflecting an assumption built into the original forward model. Although such inverse-theoretical reconstruction would not constitute definitive proof of the HEZ, it would substantially strengthen the hypothesis by showing that an HEZ-like structure can emerge even when its spatial pattern is not explicitly imposed at the reconstruction stage. Furthermore, these inverse-theoretical approaches may help test hypotheses originally formulated in forward-model studies such as ours and may also serve as a useful means of validation. In this sense, our AI-assisted conceptual inverse-theoretical virtual reconstruction suggested a structure that resembles the HEZ without explicitly prescribing that pattern beforehand, supporting the view that the finding is not solely dependent on the assumptions of the original forward model.

The dual-dissipative structural hypothesis of an anterior HEZ and a posterior pump-coupling zone

When considering the quasi-two-dimensional nature of the HEZ, it is theoretically natural to regard the HEZ immediately beneath Bowman's layer as an anterior boundary-like dissipative surface. In this context, the endothelium–Descemet membrane complex, or the posterior stromal terminal condition, may be regarded as the corresponding posterior boundary condition. This interpretation does not imply the presence of a rigid anatomical wall or a sharply reflective surface. Rather, it suggests that the anterior HEZ may function as a boundary-like dissipative surface onto which the three-dimensional stromal state is projected and functionally encoded, only in relation to a posterior regulatory boundary that defines the axial domain of the corneal stroma. Interestingly, AI-assisted virtual simulations based on inverse scattering theory, especially those conceptually related to the approaches of Kimura and Cakoni–Colton, also suggested a more complex corneal structure. In some datasets, particularly those related to corneal endothelial observations, the reconstructed patterns did not show only an anterior HEZ-like region. They also suggested a posterior pump-coupling zone, or a posterior endothelial-associated dissipative boundary. At first, this posterior emphasis may appear inconsistent with the standard anterior HEZ model. However, it does not necessarily contradict the HEZ hypothesis. Rather, it suggests that the cornea may function as a multilayered dissipative system. In this view, endothelial pump activity provides a posterior regulatory and boundary-conditioning mechanism, while the anterior HEZ acts as a major site of stromal flow organization, Marangoni-like coupling, and entropy dissipation. Therefore, the posterior endothelial-associated component does not weaken the significance of the anterior HEZ. Instead, it expands the model into a broader corneal transport theory. Large-scale stromal organization may depend on functional coupling between a posterior endothelial pump-related boundary and an anterior entropy-producing HEZ-like region. In this interpretation, the corneal endothelium does not simply act as a mechanical pump producing a unidirectional bulk flow across the entire corneal thickness. Rather, it functions as a posterior regulatory and energy-consuming boundary that maintains ionic, osmotic, and hydration conditions at the interface with the aqueous humor. These posterior boundary conditions may generate local gradients in hydration pressure, solute concentration, and electro-osmotic coupling within the posterior stroma. Such gradients could contribute to slow secondary stromal transport or recirculating components through bound water, free water, and hydration shells surrounding glycosaminoglycans. The

anterior HEZ may then organize these posteriorly conditioned fluctuations through Marangoni-like coupling and local dissipative structuring. Thus, a slow posterior-to-anterior secondary stromal transport or recirculating component, rather than a simple one-way bulk flow across the entire corneal thickness, may provide a functional pathway linking the posterior pump-coupling boundary to the anterior HEZ. A fraction of aqueous humor-derived or endothelial-conditioned water could participate in this stromal recirculation, carrying thermal, solute, and structural fluctuations toward the anterior HEZ. In the HEZ region, these fluctuations may be organized into dissipative flow patterns and redirected toward external boundaries. Taken together, these findings support a dual-dissipative model of corneal homeostasis. The cornea may be understood as a functionally coupled system composed of an anterior HEZ, a solute-dominant Marangoni-coupling region, and a posterior endothelial pump-coupling boundary. In this interpretation, endothelial pump activity serves as a major posterior regulatory and energy-consuming boundary condition, whereas the anterior HEZ acts as a higher-order organizer of stromal flow and entropy dissipation. Thus, the coexistence of anterior and posterior features should be viewed not as a contradiction, but as indirect support for a dual-dissipative structure.

Overall Conclusion

The integration of the High Entropy-Production Zone (HEZ) hypothesis with Marangoni-like fluid dynamics offers a potentially important new perspective for understanding corneal physiology. Rather than viewing the cornea solely through the lens of a homogeneous pump-leak model, this perspective suggests that the tissue may function as a highly organized thermodynamic system. In this view, the anterior stroma is not simply a passive structural layer, but a dynamic region in which concentrated metabolic activity generates the thermal and solutal gradients needed to sustain organized fluid transport. The qualitative agreement between the conceptual AMR-DNS model and the in vivo observations reported by Inoue et al. supports the possibility that intracorneal swirling convection is driven primarily by solutal Marangoni-like forces. This dual-engine model, in which passive gradient-driven convection complements ATP-dependent endothelial pumping, may reflect an especially efficient strategy for long-term maintenance of transparency in an avascular tissue. Irrespective of whether the HEZ hypothesis is ultimately validated as a physiological mechanism in the native human cornea, it may also provide a conceptual basis for the future design of artificial corneas capable of supporting organized fluid transport,

thermodynamic stability, and long-term optical transparency. Moreover, extending this idea into a quantum thermodynamic formulation using Lindblad dynamics and von Neumann entropy broadens the significance of the HEZ beyond local physiology alone. The preservation, across classical and quantum formulations, of key features such as solute dominance, thermal stabilization, and the optimal depth range of 50–100 μm suggests an intriguing form of cross-scale consistency. In this sense, macroscopic biological order may be closely linked to microscopic dissipative processes, including quantum information loss. The cornea may therefore represent a particularly compelling example of a Dissipative Decoherence Structure, in which irreversible microscopic dissipation is not merely tolerated but may contribute directly to organized macroscopic transport. This perspective also evokes, in a broader physical sense, not only universal thermodynamic principles concerning the emergence of order from dissipation in open, non-equilibrium systems, but also the evolutionary dimension of visual function, in which transparent and highly ordered ocular tissues may have been selected to sustain efficient light transmission under continuous metabolic and thermodynamic constraints. With further experimental and mathematical validation, together with advanced imaging and biophysical measurement techniques, the dual-dissipative structural hypothesis of an anterior HEZ, Marangoni-like coupling, and a posterior pump-coupling zone may serve as a useful integrated theoretical model for clarifying how the cornea sustains such a remarkable balance between local dissipation and global order, and how it maintains $\Delta S_{in} - \Delta S_{out} \leq 0$ while preserving corneal transparency for more than 100 years.

Abass A, et al. Transverse depth-dependent changes in corneal collagen lamellar orientation and distribution. J R Soc Interface. 2015;12(104):20140717. doi:10.1098/rsif.2014.0717.

Park S, et al. Solutal Marangoni effect determines bubble dynamics during electrocatalytic hydrogen evolution. Nat Chem. 2023;15:1532–1540.

Gsell S, et al. Marangoni-like tissue flows enhance symmetry breaking of embryonic

organoids. Nat Phys. 2025;21:644–653.

Inoue T, et al. Horizontal intracorneal swirling water migration indicative of corneal endothelial function. Invest Ophthalmol Vis Sci. 2014;55:8006–8014.

Cheng X, Pinsky PM. The balance of fluid and osmotic pressures across active biological membranes with application to the corneal endothelium. PLoS One. 2015;10(12):e0145422. doi:10.1371/journal.pone.0145422.

Müller B, Schäfer A. Entropy production in high energy processes. arXiv preprint arXiv:hep-ph/0306309v2. 2003.

Ptaszyński K, Esposito M. Quantum and classical contributions to entropy production in fermionic and bosonic Gaussian systems. PRX Quantum. 2023;4(2):020353.

Caprini L, et al. Ultrafast entropy production in pump-probe experiments. Nat Commun. 2024;15:94.

Kimura's inverse scattering field theory. https://www.kurims.kyoto-u.ac.jp/~kyodo/kokyuroku/contents/pdf/2186-10.pdf

Cakoni and Colton's qualitative methods in inverse scattering theory. https://sites.math.rutgers.edu/~fc292/Cakoni-Colton-Book.pdf

https://doi.org/10.21203/rs.3.rs-7456650/v2
https://doi.org/10.21203/rs.3.rs-7633016/v2

This personal view proposes a new way of understanding corneal function using thermodynamic principles,
but these ideas are theoretical and not yet proven through experiments or in vivo validation.

Yasushi Sonoda
Initial release: April 2026